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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/821,883	03/30/2001	Reiner Laus	7636-0022.30	5347

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EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 10/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/821,883	LAUS ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *12-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 9-11* is/are rejected.

7)☒ Claim(s) *7 and 8* is/are objected to.

8)☒ Claim(s) *1-19* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply* .

DETAILED ACTION

1. The election with traverse filed October 1, 2002 in Paper No. 9 is acknowledged and has been entered. Applicants have elected the invention of group I, claims 1-11, as set forth in the restriction of the Office action mailed July 2, 2002 (Paper No. 7).

2. The amendment filed June 30, 2003 in Paper No. 13 is acknowledged and has been entered.

3. Claims 1-19 are pending in the application. Claims 12-19 have been withdrawn from further consideration pursuant to 37 CFR § 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicants timely traversed the restriction (election) requirement in Paper No. 9.

4. Claims 1-11 are currently under prosecution.

Election/Restrictions

5. Applicants' grounds of traversal of the restriction set forth in the Office action mailed July 2, 2002 (Paper No. 7) have been carefully considered, but not found persuasive. Applicants have argued that the restriction is improper because although the inventions of groups I and IV are distinct, searching and examining both inventions would not constitute an additional burden. Contrary to Applicants' assertions, the search that would be required to examine the invention of group IV is not co-extensive with the search required to examine the invention of group I. Therefore, searching and examining both inventions would constitute a serious burden. Therefore, the requirement is deemed proper and made FINAL.

Nonetheless, Applicants are advised that process claims that depend from or include all the limitations of an *allowable* product claim may be rejoined in accordance with MPEP § 821.04.

Compliance to the Sequence Rules under 37 CFR §§ 1.821-1.825

6. The communication filed June 30, 2003 is not fully responsive to the Office communication mailed April 28, 2003 for the reasons set forth on the attached Notice To Comply With The Sequence Rules. Applicants must comply with the requirements of the sequence rules (37 CFR §§ 1.821 - 1.825) before the application can be further examined under 35 U.S.C. §§ 131 and 132.

Applicants are given the same period of time within which to reply to this Office action to correct the deficiency so as to comply with the sequence rules (37 CFR §§ 1.821 - 1.825) in order to avoid abandonment of the application under 37 CFR § 1.821(g).

Specification

7. The specification is objected to because the use of numerous improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Examples of improperly demarcated trademarks include Genbank™ (page 9), Nalgene™ (page 17), Forma Scientific™ (page 17), Clontech™ (page 23), Invitrogen™ (page 23), GIBCO BRL (page 24), and Sigma™ (page 24).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and

accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

8. The disclosure is objected to because of the following informalities: "GENBANK" is misspelled at page 10, in lines 1-5 of the footnotes, and at page 12 in the footnote. Appropriate correction is required.

Claim Objections

9. Claims 7 and 8 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1-4, 6, and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Burke et al. (*Oncogene* **14**: 687-696, 1997), as evidenced by Fendly et al. (*J. Biol. Response Mod.* **9**: 49-455, 1990) and Reiser et al. (*Urol. Int.* **63**: 151-159, 1999; abstract only - PUBMED ID NO. 10738185).

Claim 1 is drawn to a fusion protein, which is a protein comprising a polypeptide or protein antigen sequence component and a sequence component, the latter of which is derived from the intracellular domain of the HER-2 protein, with the provision that the polypeptide or protein antigen sequence component is

immunogenic and capable of eliciting a cellular immune response. The claim encompasses proteins in which the first and second components are directly or indirectly adjoined, such that the fusion protein may comprise an intervening sequence that separates the first and second sequence components. For example, the claim encompasses one of the particularly claimed embodiments of claim 7, namely "HER500*", which is a fusion protein comprising a first and a second component adjoined by the intervening amino acid sequence of SEQ ID NO: 22. Furthermore, the claim encompasses fusion proteins in which a first component comprises the mature HER-2 distal extracellular domain sequence presented as SEQ ID NO: 23 and/or in which a second component is derived from a HER-2 intracellular domain sequence component having the sequence presented as SEQ ID NO: 25. For example, the claim encompasses one of the particularly claimed embodiments of claim 7, namely "HER500", which is a fusion protein comprising a mature HER-2 membrane distal extracellular domain sequence, which consists of the sequence gly-ala-ala-SEQ ID NO: 23.

Burke et al. teach a fusion protein that comprises a polypeptide or protein antigen sequence component and a sequence component derived from the intracellular domain of the HER-2 protein. The polypeptide or protein antigen sequence component of the fusion protein of the prior art is the extracellular domain of the HER-2 protein. The sequence component derived from the intracellular domain of the HER-2 protein of the fusion protein is the intracellular domain of the HER-2 protein. The polypeptide or protein antigen sequence component and the sequence component derived from the intracellular domain of the HER-2 protein of the fusion protein of the prior art are adjoined by a mutant transmembrane domain sequence, as shown in Figure 1 of Burke et al.

Fendly et al. teaches that the extracellular domain of HER-2 is immunogenic and capable of eliciting a cellular immune response, as evidenced by delayed-type hypersensitivity testing. The immunogenicity of the extracellular domain of HER-2 and a fusion protein comprising the extracellular domain of HER-2 is an inherent property of the proteins. In view of the teachings of Fendly

et al., the fusion protein of the prior art is reasonably expected to elicit a cellular immune response to the polypeptide or protein antigen sequence component of the fusion protein, which in this instance is the extracellular domain of HER-2. Although Fendly et al. does not teach that the delayed-type hypersensitivity observed was induced by dendritic cells, the fusion protein of the prior art is expected to be capable of eliciting dendritic cell-induced, delayed-type hypersensitivity, or a T cell-mediated immune response to the extracellular domain of the HER-2 protein, because Rieser et al., for example, teaches that antigen-loaded dendritic cells can induce delayed-type hypersensitivity to the antigen. The ability of the fusion protein of the prior art to elicit a dendritic cell-induced, T cell-mediated immune response is an inherent property. If dendritic cells were pulsed, or loaded with the fusion protein of the prior art, in view of the teachings of Rieser et al., it is reasonable to expect the immune response elicited to be a dendritic cell-induced, T cell-mediated immune response, as required by claim 9.

Accordingly, absent a showing of any difference, the fusion protein of the prior art is deemed the same as the fusion protein of the claims. The Office, however, does not have the facilities for examining and comparing Applicants' product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics as the claimed fusion protein. In the absence of evidence to the contrary, the burden is upon the applicant to prove that a claimed product is different than a product taught by the prior art.

12. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Feinmesser et al. (*Oncogene* **12**: 2725-2730, 1996), as evidenced by van Lieshout et al. (*Japanese Journal of Cancer Research* **90**: 81-85, 1999) and Schechtman et al. (*Parasite Immunology* **23**: 213-217, 2001).

Feinmesser et al. teaches a fusion protein comprising a polypeptide or protein antigen sequence component, namely glutathione-S-transferase (GST),

and further comprising a sequence component derived from the intracellular domain of the HER-2 protein, which intracellular domain has the sequence presented as SEQ ID NO: 25, namely amino acid residues 1005-1125, or residues 1126-1255 of the intracellular domain of HER-2. Feinmesser et al. teaches the fusion protein is produced by translation of a continuous nucleic acid coding sequence.

As evidenced by van Lieshout et al., the polypeptide or protein antigen sequence component of the fusion protein of the prior art, namely GST is associated with tumor cells. More particularly, van Lieshout et al. teaches an association between the expression level of GST in esophageal epithelial tissue and the incidence of cancer in that tissue.

The fusion protein of the prior art is deemed the same as the immunostimulatory fusion protein of the claims, absent a showing of any difference, because the fusion protein of the prior is reasonably expected to be immunostimulatory and to elicit a cellular immune response to the polypeptide or protein antigen sequence component of the fusion protein. Schechtman et al. teaches a cellular immune response was detected in mice immunized with GST. The immunogenicity of GST and a fusion protein comprising GST is an inherent property of the proteins. In view of Schechtman et al., the fusion protein of the prior art is reasonably expected to elicit an immune response to the polypeptide or protein antigen sequence component of the fusion protein, namely GST.

The Office does not have the facilities for examining and comparing Applicants' product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics as the claimed fusion protein. In the absence of evidence to the contrary, the burden is upon the applicant to prove that a claimed product is different than a product taught by the prior art.

13. Claims 1, 2, 5, and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Tuzi et al. (*Biochem. Soc. Trans.* **16**: 675-677, 1988), as

evidenced by Wada et al. (*Proceedings of the National Academy of Sciences of the USA* **94**: 12557-12561, 1997).

Tuzi et al. teaches a fusion protein comprising a polypeptide or protein antigen sequence component, namely keyhole limpet haemocyanin (KLH), and further comprising a sequence component derived from the intracellular domain of the HER-2 protein, which has the sequence presented as SEQ ID NO: 25, namely amino acid residues 1215-1225 of the intracellular domain of HER-2. Tuzi et al. teaches chemical coupling using glutaraldehyde produced the fusion protein.

The fusion protein of the prior art is deemed the same as the immunostimulatory fusion protein of the claims, absent a showing of any difference, because the fusion protein of the prior is reasonably expected to be immunostimulatory and to elicit a cellular immune response to the polypeptide or protein antigen sequence component of the fusion protein. Wada et al. teaches KLH is effective to elicit a dendritic cell-induced, T cell-mediated immune response. The immunogenicity of KLH and a fusion protein comprising KLH is an inherent property of the proteins. In view of Wada et al., the fusion protein of the prior art is reasonably expected to be effective to elicit a cellular immune response to the polypeptide or protein antigen sequence component of the fusion protein, namely KLH.

Again, the Office does not have the facilities for examining and comparing Applicants' product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics as the claimed fusion protein. In the absence of evidence to the contrary, the burden is upon the applicant to prove that a claimed product is different than a product taught by the prior art.

14. Claims 1-4, 6, and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent No. 5,846,538 A.

The term "fusion protein" does not appear to be explicitly defined in the specification to exclude a recombinant intact HER-2 protein produced by the translation of a continuous nucleic acid coding sequence, which protein comprises a polypeptide or protein antigen sequence component and a sequence component derived from the intracellular domain of the HER-2 protein. Moreover, the polypeptide or protein antigen sequence component of the fusion protein need not be heterologous. For example, the fusion protein of claim 6 comprises polypeptide or protein antigen sequence component, which is the extracellular domain of the HER-2 protein.

US Patent No. 5,846,538 A ('538) teaches a method for treating a malignancy of the breast, ovary, colon, lung, or prostate comprising immunizing a human with a protein comprising all or part of the intracellular domain of the HER-2 protein. At column 13, '538 teaches an intact HER-2 protein may be used in practicing the disclosed invention. The intact HER-2 protein of the prior art comprises a polypeptide or protein antigen sequence component, namely the extracellular and transmembrane domains of the HER-2 protein, and a sequence component derived from the intracellular domain of the HER-2 protein, namely the intracellular domain of the HER-2 protein. '538 teaches the extracellular domain of the HER-2 protein, or peptides derived therefrom, are immunogenic and capable of eliciting a cellular immune response to the extracellular domain of the HER-2 protein.

'538 teaches HER-2, and it extracellular domain, is associated with cancer. '538 teaches the protein may be produced by the translation of a continuous nucleic acid coding sequence, which has been cloned into an expression vector.

The term "dendritic cell" is defined at page 5 of the specification to include a subset of antigen-presenting cells capable of activating CD8+ cytotoxic T cells (CTL). '538 teaches HER-2-specific CD8+ T cell-mediated immune responses can be elicited by the use of autologous antigen-presenting cells transfected with an expression vector that produces the relevant HER-2/neu protein as stimulator

cells. Accordingly, absent a showing of any difference, the intact HER-2 protein of the prior art is deemed the same as the fusion protein of claim 9, because it appears that the intact HER-2 protein is capable of eliciting a dendritic cell-induced, T cell-mediated immune response to the extracellular domain of the HER-2 protein.

The Office does not have the facilities for examining and comparing Applicants' product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics as the claimed fusion protein. In the absence of evidence to the contrary, the burden is upon the applicant to prove that a claimed product is different than a product taught by the prior art.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 1-6 and 9-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 5,846,538 A in view of US Patent No. 6,080,409 A (cited by Applicants), Ossevoort et al. (*J. Immunother. Emphasis Tumor Immunol.* **18**: 86-94, 1995), and Toes et al. (*Journal of Immunology* **160**: 4449-4456, 1998), as evidenced by Inaba et al. (*Journal of Experimental Medicine* **172**: 631-640, 1990) and Wadhwa et al. (*Clinical Cancer Research* **5**: 1353-1361, 1999).

The claims encompass a fusion protein that is a protein comprising a heterologous polypeptide or protein antigen sequence component and a sequence component derived from the intracellular domain of the HER-2 protein.

US Patent No. 5,846,538 A ('538) teaches a protein comprising all or part of the intracellular domain of the HER-2 protein and a method for treating a malignancy of the breast, ovary, colon, lung, or prostate comprising immunizing a human with an immunogenic composition comprising this protein. '538 teaches that the protein may be the intact HER-2 protein. '538 teaches the extracellular domain of the HER-2 protein, or peptides derived therefrom, are immunogenic and capable of eliciting a cellular immune response to the extracellular domain of the HER-2 protein. '538 teaches HER-2-specific CD8+ T cell-mediated immune responses can be elicited by the use of autologous antigen-presenting cells transfected with an expression vector that produces the relevant HER-2/neu protein as stimulator cells.

Additionally, '538 teaches addition of an immunostimulatory substance such as GM-CSF to the immunogenic composition is desirable. If a peptide is used as the immunogen in practicing the method, '538 teaches that it may be desirable to couple the protein to a carrier substance.

However, '538 does not teach a fusion protein that is a protein comprising a heterologous polypeptide or protein antigen sequence component and a sequence component derived from the intracellular domain of the HER-2 protein.

US Patent No. 6,080,409 A teaches a method for treating breast cancer comprising inducing in a mammalian subject a T cell-mediated cellular immune response to a soluble HER-2 protein, which method comprises isolating autologous antigen-presenting cells from the subject, exposing the cells *in vitro* to a conjugate of GM-CSF and the soluble HER-2 protein to activate the cells, and administering the activated cells to the subject. More particularly, '409 teaches the activated antigen-presenting cells to be administered to the subject are activated dendritic cells. In addition, '409 teaches the conjugate can be produced by translation of a continuous nucleotide coding sequence; alternatively, '409 teaches conjugates can be formed by chemical means, such as by conventional coupling techniques.

Furthermore, '409 discloses that administering activated dendritic cells to a subject can elicit an HLA class I-restricted cytotoxic T cell (CTL) immune response, whereas induction of such a response by administering pure soluble protein antigens *in vitro* had not been reported. '409 teaches the use of antigen-presenting cells stimulated by GM-CSF/HER-2 antigen fusion proteins yields superior results to other approaches, such as the use of peptide-pulsed antigen-presenting cells. Moreover, '409 discloses that the use of GM-CSF/HER-2 antigen fusion proteins can overcome some of the limitations of other approaches, such as delivery of proteins incorporated into liposomes or by osmotic shock, which are relatively ineffective because of the inherent toxicity of these treatments to dendritic cells. '409 teaches GM-CSF/HER-2 antigen fusion proteins are capable of inducing immunity toward multiple epitopes and at the same time, preserve and enhance viability and function of the dendritic cell.

Ossevoort et al. teaches dendritic cells pulsed with a cytotoxic T lymphocyte (CTL) epitope-based peptide can elicit a T cell-mediated immune response to an antigen. In fact, Ossevoort et al. teach that the pulsed dendritic cells more effectively serve as a tumor-specific vaccine than the peptide alone, since, whereas two doses of the peptide were required to elicit protection against outgrowth of antigen-expressing tumor cells, only one dose of peptide pulsed dendritic cells sufficed.

Toes et al. teaches that peptide vaccination can induce immune tolerance by tolerizing T cells to paradoxically enhance the growth of a tumor. However, Toes et al. teaches that tolerization of cytotoxic T lymphocytes (CTL) by peptide vaccination can be avoided by the use of peptide-pulsed dendritic cell vaccines instead. Toes et al. teach that it is of crucial importance to avoid T cell tolerization through peptide vaccination in a clinical setting. Toes et al. therefore concludes, because dendritic cells can revert the CTL-tolerizing potential of a synthetic peptide vaccine into a vaccine capable of inducing protective antitumor immunity, a rationale for using dendritic cells as the primary vehicles of choice for the development of synthetic peptide-based vaccines is provided.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have prepared an immunostimulatory fusion protein composition comprising dendritic cells activated by *in vitro* exposure to an immunostimulatory fusion protein comprising a polypeptide, namely GM-CSF, and minimally a sequence component derived from the intracellular domain of the HER-2 protein, if not the intact HER-2 protein, because both '538 and '409 teach that immunizing a subject using an immunogenic composition comprising an HER-2 antigen can be effective to treat breast cancer, but moreover because '409 teaches that a GM-CSF/HER-2 antigen fusion protein can be used advantageously to preserve and enhance the viability and function of the dendritic cell, because Ossevoort et al. teaches that antigen pulsed dendritic cell vaccines more effectively elicit a cellular immune response against tumor cells expressing the antigen, and because Toes et al. teaches that the use of antigen pulsed dendritic cell vaccines avoids the limitations of peptide vaccination to more effectively stimulate a protective antitumor immune response. One of ordinary skill in the art at the time the invention was made would have been motivated to have done so because, for example, Ossevoort et al. and Toes et al. teaches an immunostimulatory fusion protein composition comprising dendritic cells activated by *in vitro* exposure to an immunostimulatory fusion protein can be used more effectively than immunizing a subject with the immunostimulatory fusion protein alone and because '409 teaches the use of antigen-presenting cells stimulated by GM-CSF/HER-2 antigen fusion proteins yields superior results to other approaches, such as the use of peptide-pulsed antigen-presenting cells.

The immunostimulatory fusion protein composition comprising dendritic cells activated by *in vitro* exposure to an immunostimulatory fusion protein comprising a polypeptide, namely GM-CSF, and minimally a sequence component derived from the intracellular domain of the HER-2 protein is expected to comprise the immunostimulatory fusion protein. This expectation is reasonable in view of the teachings of Inaba et al. Inaba et al. teaches that dendritic cells can be activated by pulsing the cells with intact antigens and that

the pulsed and activated dendritic cells can be administered to mice to prime a T cell-mediated immune response to the antigen. Inaba et al. teaches that the antigen used to pulse dendritic cells, which were later administered to mice, can be visualized within the endocytic vacuoles of the antigen-pulsed dendritic cells, suggesting that dendritic cells are able to present antigens over a several day period *in situ*. Accordingly, the immunostimulatory fusion protein composition rendered obvious by the prior art, which comprises dendritic cells activated by *in vitro* exposure to an immunostimulatory fusion protein, is deemed the same as the immunostimulatory fusion protein composition of claim 11, which comprises the immunostimulatory fusion protein composition of claim 10 and further comprises the immunostimulatory fusion protein of claim 1.

As evidenced by Wadhwa et al., GM-CSF is immunogenic and capable of eliciting a cellular immune response. Accordingly, the fusion protein of the prior art is reasonably expected to elicit a cellular immune response to the polypeptide or protein antigen sequence component of the fusion protein, which in this instance is GM-CSF.

Accordingly, absent a showing of any obvious difference, the fusion protein of the prior art, and the composition thereof, is deemed the same as the fusion protein of the claims, and the claimed composition thereof. The Office, however, does not have the facilities for examining and comparing Applicants' product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics as the claimed fusion protein. In the absence of evidence to the contrary, the burden is upon the applicant to prove that a claimed product is different than a product taught by the prior art.

Conclusion

16. The subject matter of claims 7 and 8 is free of the art, but claims 7 and 8 are objected to as being dependent upon rejected base claims. Therefore, no claims are allowed.

17. The art made of record and not relied upon is considered pertinent to Applicants' disclosure. Sorkin et al. teaches a fusion protein comprising the extracellular domain of EGFR and the intracellular domain of HER-2. Mitchell et al. teaches bone marrow-derived dendritic cell progenitors capture exogenous antigen for class I presentation. US Patent No. 6,406,681 B1 teaches a fusion protein comprising GM-CSF and a tissue-specific tumor antigen, such as HER-2. US Patent No. 6,544,518 B1 teaches a fusion protein comprising all or part of the intracellular domain of HER-2 and all or part of the extracellular domain of HER-2. Shimizu et al. teaches enhancement of dendritic cell-based vaccines by the addition of foreign helper protein. Timmerman et al. teaches enhancement of the immunogenicity of a pulsed dendritic cell vaccine by linkage of foreign carrier protein to a self-tumor antigen. Vidovic et al. teaches antitumor vaccination using HER-2-derived antigens, which are embodiments of the presently claimed invention. Foy et al. (2002) reviews designing HER-2 vaccines. Foy et al. (2001) teaches vaccination with portions of HER-2. Disis et al. (1997) reviews HER-2 as a target for antigen-specific immunotherapy of cancer. Pucetti et al. teaches that dendritic cells can induce delayed-type hypersensitivity, a T cell-mediated immune response. Toes et al. (1996) teaches peptide vaccination can lead to enhanced tumor growth through an induction of specific T-cell tolerance. Steinman reviews the dendritic cell system and its role in immunogenicity.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J Rawlings
STEPHEN RAWLINGS

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
September 30, 2003

Notice to Comply	Application No.	Applicant(s)	
	09/821,883	LAUS ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☐ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: The specification discloses sequences not properly identified by the sequence identification number corresponding to the matching sequence in the sequence listing; see page 4, line 17; page 17, line 21; and page 24, lines 11 and 13. Applicants should amend the specificaiton to recite the appropriate SEQ ID NO. after each disclosure of sequence in accordance with 37 CFR 1.821-1.825.

Applicant Must Provide:

☐ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☐ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☐ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

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